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1. REPORT NUMBER M14/86		2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Oral pyridostigmine administration in rats: effects a thermoregulation, clinical chemistry, and performance in the heat.		5. TYPE OF REPORT & PERIOD COVERED	
7. AUTHOR(s) R. Francesconi, R. Hubbard, C. Matthew, N. Leva J. Young, and V. Pease		6. PERFORMING ORG. REPORT NUMBER	
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Research Institute of Environmental Medicine, Natick, MA 01760-5007		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 3M162734A875 64386101042	
11. CONTROLLING OFFICE NAME AND ADDRESS		12. REPORT DATE	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		13. NUMBER OF PAGES	
		15. SECURITY CLASS. (of this report) UNCLAS	
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report) DISTRIBUTION A: Approved for public release; distribution is unlimited.			
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)			
18. SUPPLEMENTARY NOTES			
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) cholinesterase inhibition, exercise, hyperthermia, exhaustion			
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) We have recently reported that acute intraperitoneal administration of pyridostigmine bormide to rats resulted in significant decrements in physical performance in the heat, adverse thermoregulatory effects, and exacerbated elevations in several indices of heat/exercise injury. To simulate anticipated human use of this carbamate as a prophylaxis for organophosphate poisoning, pyridostigmine was dissolved in the drinking water of rats. Consumption of pyridostigmine for 7 days (n=34, 6.6 mg/day) resulted in a 23% (p<.001) reduction of circulating cholinesterase when compared with a control group (n=31)			

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## Appendix 1: Biology

### Conclusion

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Oral pyridostigmine administration in rats:  
effects on thermoregulation, clinical chemistry,  
and performance in the heat

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### Abstract

We have recently reported that acute intraperitoneal administration of pyridostigmine bromide to rats resulted in significant decrements in physical performance in the heat, adverse thermoregulatory effects, and exacerbated elevations in several indices of heat/exercise injury. To simulate anticipated human use of this carbamate as a prophylaxis for organophosphate poisoning, pyridostigmine was dissolved in the drinking water of rats. Consumption of pyridostigmine for 7 days ( $n=34$ , 6.6 mg/day) resulted in a 23% ( $p<.001$ ) reduction of circulating cholinesterase when compared with a control group ( $n=31$ ) while ingestion for 14 days ( $n=35$ , 8.9 mg/day) elicited a 39% ( $p<.001$ ) inhibition of circulating cholinesterase when compared to a second control group ( $n=33$ ). Water and food consumption, rate of weight gain, and overt behavior were unaffected by pyridostigmine consumption. When approximately half the animals in each group were exercised (9.14 m/min) in the heat ( $35^{\circ}\text{C}$ ) to hyperthermic exhaustion ( $T_{re} = 42.5-43^{\circ}\text{C}$ , rats unable to right themselves), pyridostigmine consumption for 14 days effected a significantly ( $p<.05$ ) increased rate of weight (water) loss, but no further effects on thermoregulation or performance were noted. Several minor increments were observed in clinical indices of heat/exercise injury in rats consuming pyridostigmine for 14 days. We have concluded from these studies that administration of pyridostigmine in the drinking water of animals may be a quantitative and suitable means to simulate oral consumption in humans. Further, oral dosages of pyridostigmine can probably be titrated to levels of cholinesterase inhibition which are efficacious in prophylaxis against organophosphate toxicity without significant effects on normal physiologic and metabolic processes.

## Introduction

For several years we have been quantitatively examining factors which limit the ability to work in the heat (8-10) in an exercising rat model of human heat/exercise injury (15,17). In a recent report we have demonstrated (6) that malathion-induced cholinesterase inhibition had no decremental effects on endurance capacity in the heat. In these experiments circulating cholinesterase activity was inhibited (35%) by consecutive daily dosages of malathion while physical, physiological, and thermoregulatory efficiencies were unaffected. We have been interested in the effects of cholinesterase inhibition on the ability to work in the heat since atropine, the most commonly used antidote for organophosphate poisoning (13,14), ordinarily decreases heat tolerance (2,4) through its anticholinergic potency (1,18). In fact, we have recently reported (16) that atropinized rats manifested an elevated heat storage when sedentarily exposed to an extreme heat stress (41.5°C).

Subsequently, we examined the effects of a proposed organophosphate prophylaxis (5,12), pyridostigmine, a carbamate which reversibly inhibits cholinesterase, on the ability to work in the heat (7). In these experiments consecutive doses of pyridostigmine elicited a 64% decrement in plasma cholinesterase activity. When these animals were subsequently exercised in the heat to hyperthermic exhaustion, they manifested a markedly decreased endurance which we attributed to more rapid dehydration and increased heat storage. However, in these studies (7) relatively large doses of pyridostigmine were administered by intraperitoneal injection, and the rats were exercised at a time corresponding to maximal cholinesterase inhibition.

In the current studies we have continued these earlier experiments with several important modifications. The acute pharmacological doses of pyridostigmine were replaced by oral consumption of pyridostigmine which had been dissolved in the drinking water of rats. This methodology is in keeping with the intended usage of this drug as a prophylaxis for organophosphate toxicity.

#### Methods

Groups of adult male Sprague-Dawley rats (Charles River, 225-275g) were housed singly in wire bottomed cages in windowless rooms (21°C) with food (Ralston-Purina Rodent Chow) available ad lib. Control rats had unlimited access to drinking (tap) water while experimental animals had similar access to water containing Mestinox® (pyridostigmine bromide, 240 mg/930 ml, Roche Labs, Nutley, NJ) as their sole fluid source for 7 or 14 days. During these intervals rats were monitored carefully for food and water consumption to determine the effects, if any, of pyridostigmine consumption or nutritional variables.

On the sixth or thirteenth day each rat was fitted with an indwelling silastic catheter (external jugular vein) for rapid and convenient blood sampling. This minor intrusive procedure had no apparent effects on the subsequent ability to exercise in the heat. On the following day each animal in the exercising group was weighed and fitted with a rectal probe (Model 701, Yellow Springs Inst. Yellow Springs, OH) inserted to a depth of 6 cm, and a surface probe (Yellow Springs Model 709) was secured midlength on the tail. Under restraint a small sample of blood (0.8ml) was obtained from the indwelling catheter to establish levels of plasma cholinesterase as well as the clinical chemical indices of heat/exercise injury (10,15,17).

Hematocrits were immediately quantitated, and the remainder of the sample was centrifuged (10000 g, 4°C, 20 min), and the plasma removed, frozen, and stored (-20°C) for subsequent analysis.

Approximately one half the total rats in each group were then quickly removed to a large (3m x 4m x 2m) stainless steel chamber (35 ± 0.5°C, 30-40% rh) where they exercised (9.14 m/min, level treadmill) until hyperthermic exhaustion (Tre = 42.5-43°C, animal unable to right itself) ensued. During the treadmill interval rectal (Tre) and skin (Tsk) temperatures were monitored on a minute-by-minute basis. Immediately upon removal from the treadmill a second blood sample was withdrawn, and the rat was returned to the holding room, probes removed, and weights again recorded to determine the water loss during the experimental procedure. The post-run blood sample was treated identically as the first. The frozen plasma was ultimately assayed for a variety of clinical chemical indices of heat/exercise injury as well as cholinesterase activity.

Prepared test kits (Sigma, St. Louis, MO), modified for smaller volumes and continuous monitoring of optical density, were used to assess plasma cholinesterase activity. Circulating glucose concentrations were quantitated using Worthington Statzyme test kits and lactate with kits obtained from Sigma; all assays were executed after methods described in the respective technical bulletins. Potassium (K<sup>+</sup>) and sodium (Na<sup>+</sup>) were quantitated by flame photometry (Radiometer, Copenhagen) while the remaining analyses (creatine phosphokinase, lactate dehydrogenase, creatinine, urea nitrogen) were accomplished using commercially available test kits.

Since we used separate groups of animals as control (n=31, 7 day; n=33, 14 day) for each of the experimental groups (n=34, 7 day pyrido; n=35, 14 day

pyrido), statistical analyses were performed using Student's t test for independent data (19). The null hypothesis was rejected at  $p < 0.05$ .

### Results

Fig 1 illustrates the effects of pyridostigmine consumption for 7 or 14 days on body weight gain and water and food consumption. Rats consuming pyridostigmine for 7 days ( $n=34$ ) ingested  $46.5 \pm 1.8\text{mg}$  ( $\bar{X} \pm \text{S.E.}$ ) while those on pyridostigmine for 14 days consumed  $124.3 \pm 3.1\text{mg}$  (Fig 2). Mean body weight gain calculated on a daily basis as well as food and water consumption were similar among groups; the slightly increased water consumption among the 14 day pyrido group may be associated with a slightly larger body mass among this group although, interestingly, food consumption is extremely consistent. Fig 2 illustrates the effects of 7- and 14-day consumption of pyridostigmine as well as exercise in the heat on circulating cholinesterase activity. The results indicated that consumption of pyridostigmine for 7 days (6.6 mg/day) resulted in a 23% inhibition (28.3 vs 21.8 units,  $p < .001$ ) while 14-day ingestion inhibited circulating cholinesterase by 39% (24.9 vs 15.3 units,  $p < .001$ ). The figure also illustrates that exercise in the heat to hyperthermic exhaustion did not consistently affect plasma cholinesterase activity (PRE vs POST for each group).

Prolonged pyridostigmine consumption failed to affect endurance in the heat. For example, mean treadmill times (Fig 3) for the various groups were as follows: 7-day control,  $n=15$ ,  $28.5 \pm 1.4$  min; 7-day pyrido,  $n=15$ ,  $30.0 \pm 1.95$  min, 14-day control,  $n=15$ ,  $29.5 \pm 1.9$  min; 14-day pyrido,  $n=17$ ,  $32.5 \pm 1.3$  min. Likewise, there were no marked effects on  $T_{re}$  and  $T_{sk}$  during exercise in the heat. It is interesting that rats treated with pyridostigmine for 14d (Fig 3) did manifest a statistically significant ( $p < .05$ ) increment in



mean weight (water) loss during the treadmill interval ( $15.6 \pm 0.9$  vs  $12.6 \pm 1.1$ g). However, it should also be noted that the 14-day pyridostigmine group manifested a slightly, but not significantly ( $p > .05$ ), increased body weight ( $\bar{x} = 354.4 \pm 5.4$ g) when compared to their 14-day control counterparts ( $\bar{x} = 342.3 \pm 5.2$ g).

Figs. 4-7 demonstrate the effects of prolonged consumption of pyridostigmine on the clinical chemical indices of heat/exercise injury as well as the effects of pyridostigmine consumption and exercise in the heat to hyperthermic exhaustion on these indices. The data indicate that neither 7- nor 14-day ingestion of pyridostigmine had significant effects on these variables. For example, in the blood sample taken prior to exercise in the heat it is clear that pyridostigmine consumption had no effects on circulating glucose ( $p > .05$ , Fig 4). Likewise, subsequent to exercise in the heat, there were no significant differences in plasma glucose levels among various groups. While creatine phosphokinase activity was generally increased by the heat/exercise contingency, pyridostigmine consumption had no effects on this variable. Fig 5 demonstrates that while exercise in the heat significantly ( $p < .05$ ) increased circulating levels of both lactate and lactic acid dehydrogenase, again pyridostigmine consumption had no effects ( $p > .05$ ) on these variables. The same pattern is illustrated (Fig. 6) for circulating levels of both creatinine and urea nitrogen. While exercise in the heat to hyperthermic exhaustion significantly ( $p < .05$ ) increased circulating levels of both indices, pyridostigmine consumption apparently had no effects on either. While Fig 7 illustrates no effects of pyridostigmine or heat/exercise on circulating sodium concentrations, potassium levels were significantly ( $p < .05$ ) increased by the exercise/heat contingency.

## Discussion

The impetus for the current experiments came from our earlier observation (7) that significant (64%) inhibition of circulating cholinesterase resulted in marked decremental effects on the ability to work in the heat. Further, these effects were apparently mediated through an increased cholinergic activity which gave rise to excessive water loss and increased heat gain. The present experiments were designed to investigate this phenomenon more closely since despite extensive reports on organophosphate toxicity (3,20,23), very little has appeared in the literature on the sequelae of cholinesterase inhibition by carbamate ingestion. Whereas in our first experiments we administered pharmacological doses of pyridostigmine via intraperitoneal injection, projected prophylactic usage of the carbamates calls for oral administration for up to 14 days. Consequently, we dissolved a quantity of pyridostigmine bromide in the sole source of drinking water of experimental rats. Although this concentration provided a slightly greater daily proportionate dosage than the 7-10 fold increment suggested by Freireich et al (11) for rodents vs. humans, there were no effects on food and water consumption or growth rate, and the inhibition of cholinesterase was more moderate than in our past experiment (7).

The results observed in the current experiments contrast rather sharply with our earlier work on pyridostigmine (7), but compare very closely with our earlier report on malathion administration (6). In our earlier experiment (7) we administered pyridostigmine acutely and intraperitoneally in pharmacological doses and observed marked effects on performance, thermoregulation, and clinical chemical indices of heat/exercise injury following cholinesterase inhibition of 64%. When malathion was administered

by IP injection for four consecutive days and plasma cholinesterase was inhibited by approximately 35%, we reported (6) no effects of this level of cholinesterase inhibition on performance, thermoregulation, and clinical indices of heat/exercise injury. Similarly, in the current experiments comparable levels of cholinesterase inhibition (23% and 39%) elicited no marked effects on performance, thermoregulation, and circulating indices of heat/exercise injury. These results imply that either the lowered inhibition of cholinesterase or the chronicity of the carbamate dosage or both may be responsible for the neutralization of the debilitating effects of pyridostigmine which we observed in our first report (7). It has been observed that substantial, but sign-free, doses of the carbamates must be administered before protection against organophosphate toxicity is achieved (5,12). Likewise, it is probable that a minimal level of cholinesterase inhibition must be achieved by the carbamates before physiological effects are observed.

This view is supported by our observations on water loss during exercise in the heat (6,22). In our initial report we hypothesized that the intense inhibition of circulating cholinesterase (64%) led to a greatly increased cholinergic activity resulting in a 53% increase in salivary water loss. In rats treated with pyridostigmine for 14 days (present study) our data indicated that inhibition of circulating cholinesterase by 39% elicited a 14.3% increase in the rate of water loss while a 23% inhibition of circulating cholinesterase did not affect water loss. These data are consonant with the hypothesis that the physiological and protective effects of the carbamates may be dependent upon a rather narrow range of cholinesterase inhibition.

In considering the effects of oral consumption of pyridostigmine on several clinical chemical markers of heat/exercise injury, our results indicate that the moderate cholinesterase inhibition and the chronicity of consumption again attenuated several responses which we had earlier observed following acute pharmacological doses of pyridostigmine. For example, we reported (7) that acute pyridostigmine treatment resulted in pre-run levels of glucose which were significantly elevated, and, following exercise in the heat, levels of lactate and creatine phosphokinase were also increased. In the present studies the increments were greatly attenuated. For example, following exercise in the heat mean levels of lactate (72.8 vs. 60.4 mg/dl) and glucose (21) (164.9 vs 142.7 mg/dl) manifested slightly increased trends in the rats consuming pyridostigmine for 14 days, but statistical significance was not achieved.

We have concluded from these studies that administration of pyridostigmine via the drinking water of rats represents a quantitative and efficacious means to simulate oral consumption in humans. Further, no deleterious effects were noted on weight gain or water and food consumption. Rats consuming pyridostigmine for 7 days ingested a mean level of 6.6 mg/day and manifested a cholinesterase inhibition of 23%. Those consuming pyridostigmine for 14 days imbibed an equivalent of 8.9 mg/day and circulating cholinesterase was inhibited by 39%. These levels of cholinesterase inhibition had no effects on physical performance and thermoregulation during exercise in the heat although water loss was significantly increased in the group consuming pyridostigmine for 14 days. Clinical chemical indices of heat/exercise injury were minimally affected by prolonged pyridostigmine consumption. Oral dosages of pyridostigmine can probably be titrated to levels of cholinesterase inhibition which are effective in prophylaxis against organophosphate toxicity.

### Figure Legend

Fig. 1. Effects of pyridostigmine consumption for 7 or 14 days on weight gain and food and water consumption. The 7 day control (n=31), 7 day pyridostigmine (n=34), 14 day control (n=33) and 14 day pyridostigmine (n=35) groups were monitored for each variable on a daily basis. The slightly increased water consumption in the 14 day pyridostigmine group may be due to their larger body mass at the start of the experiment.

Fig 2. Effects of pyridostigmine consumption for 7 or 14 days on circulating cholinesterase activity. In rats consuming pyridostigmine for 7 days mean cholinesterase activity was 21.8 units (unoles acetic acid formed/h/ml plasma) which represented a 23% inhibition ( $p < .001$ ) from mean control level (28.3U). Fourteen day ingestion of pyridostigmine resulted in a 39% inhibition ( $p < .001$ ) (15.3U) when compared with controls (24.9U).

Fig 3. Effects of pyridostigmine consumption on weight (water) loss during exercise in the heat and endurance. Exercise was performed on a level treadmill (9.14 m/min) at an environmental temperature of 35°C (30-40% rh) until hyperthermic exhaustion occurred (rectal temperature = 42.5-43°C, animal unable to right itself). All exercising groups consisted of 15 rats except rats consuming pyridostigmine for 14 days, n=17. Weights were recorded immediately prior and subsequent to the heat/exercise regimen.

Fig 4. Effects of pyridostigmine consumption and exercise in the heat to hyperthermic exhaustion on circulating levels of glucose and creatine

phosphokinase. PRE (0.8ml) blood samples were taken immediately prior to exercise in the heat while the POST samples were obtained at the completion of the treadmill run.

Fig 5. Effects of pyridostigmine consumption and exercise in the heat on plasma levels of lactate and lactic acid dehydrogenase. All conditions and parameters are as noted in Figs. 3 and 4.

Fig 6. Effects of pyridostigmine consumption and exercise in the heat on plasma levels of creatinine and urea nitrogen. All conditions and parameters are as noted in Figs. 3 and 4.

Fig 7. Effects of pyridostigmine consumption and exercise in the heat on plasma levels of sodium and potassium. All conditions and parameters are as noted in Figs 3 and 4.

#### Disclaimer and Acknowledgements

The authors express their gratitude to Jane DeLuca for the statistical analyses and to Susan Henry and Diane Danielski for the word processing support.

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

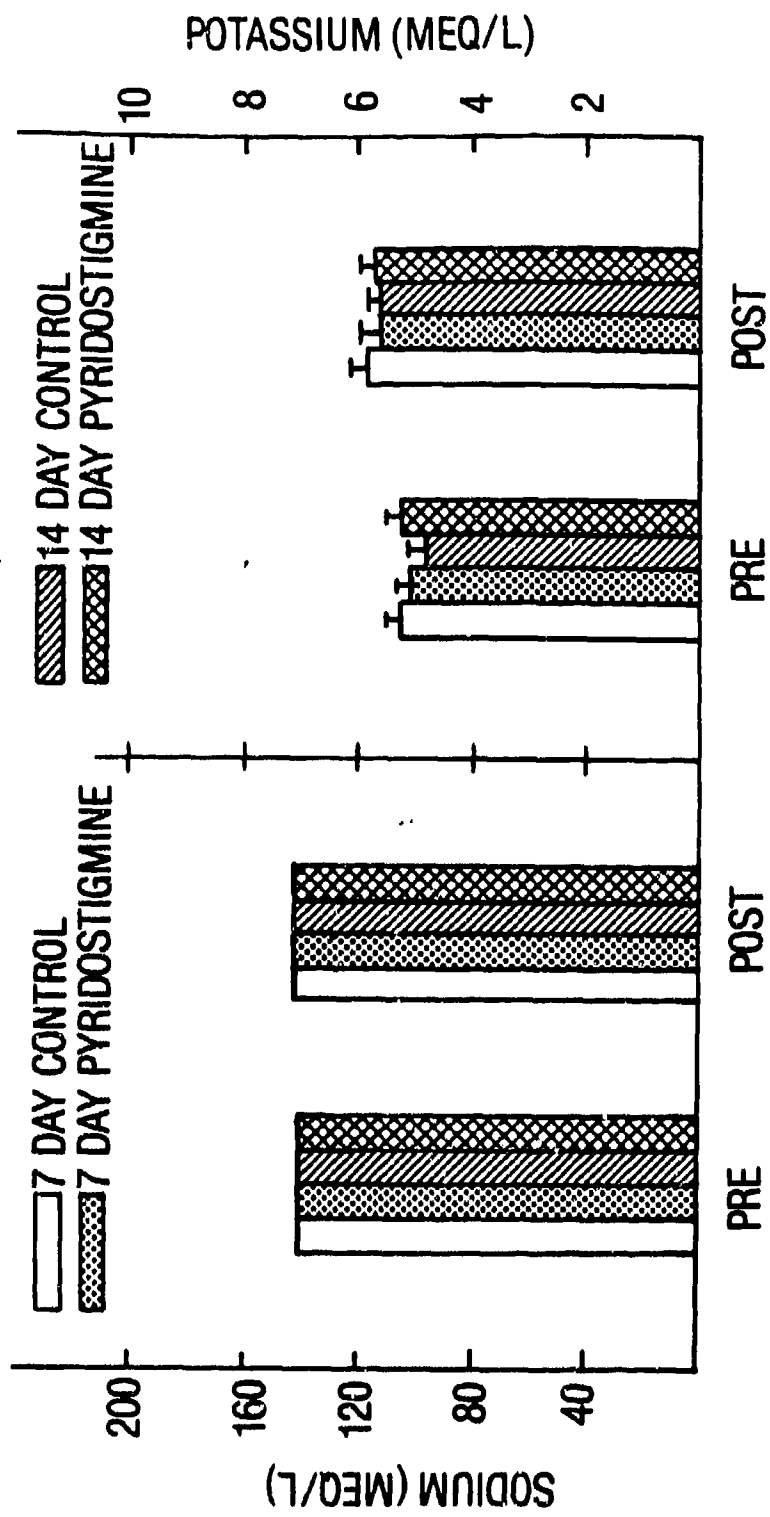
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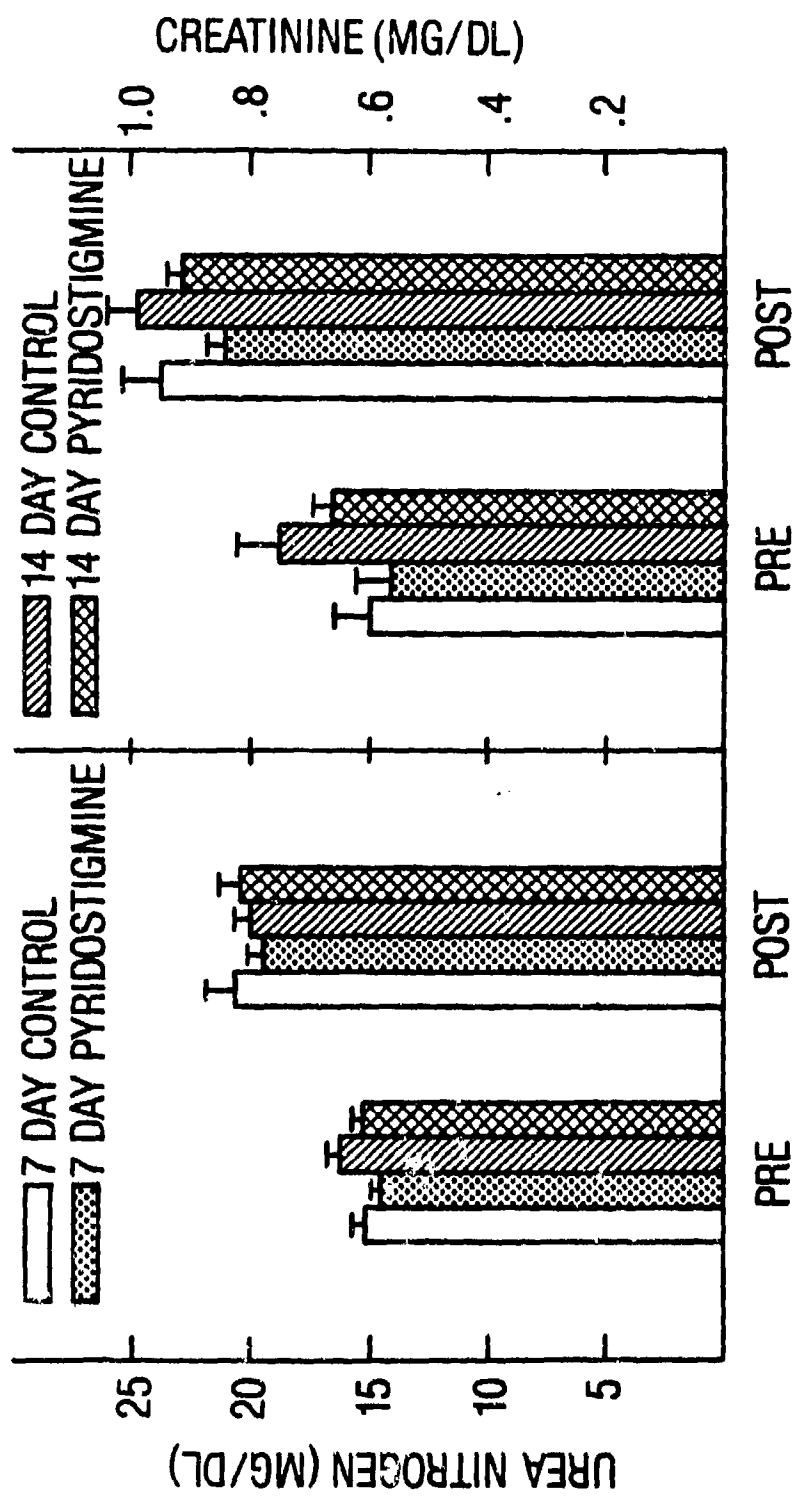
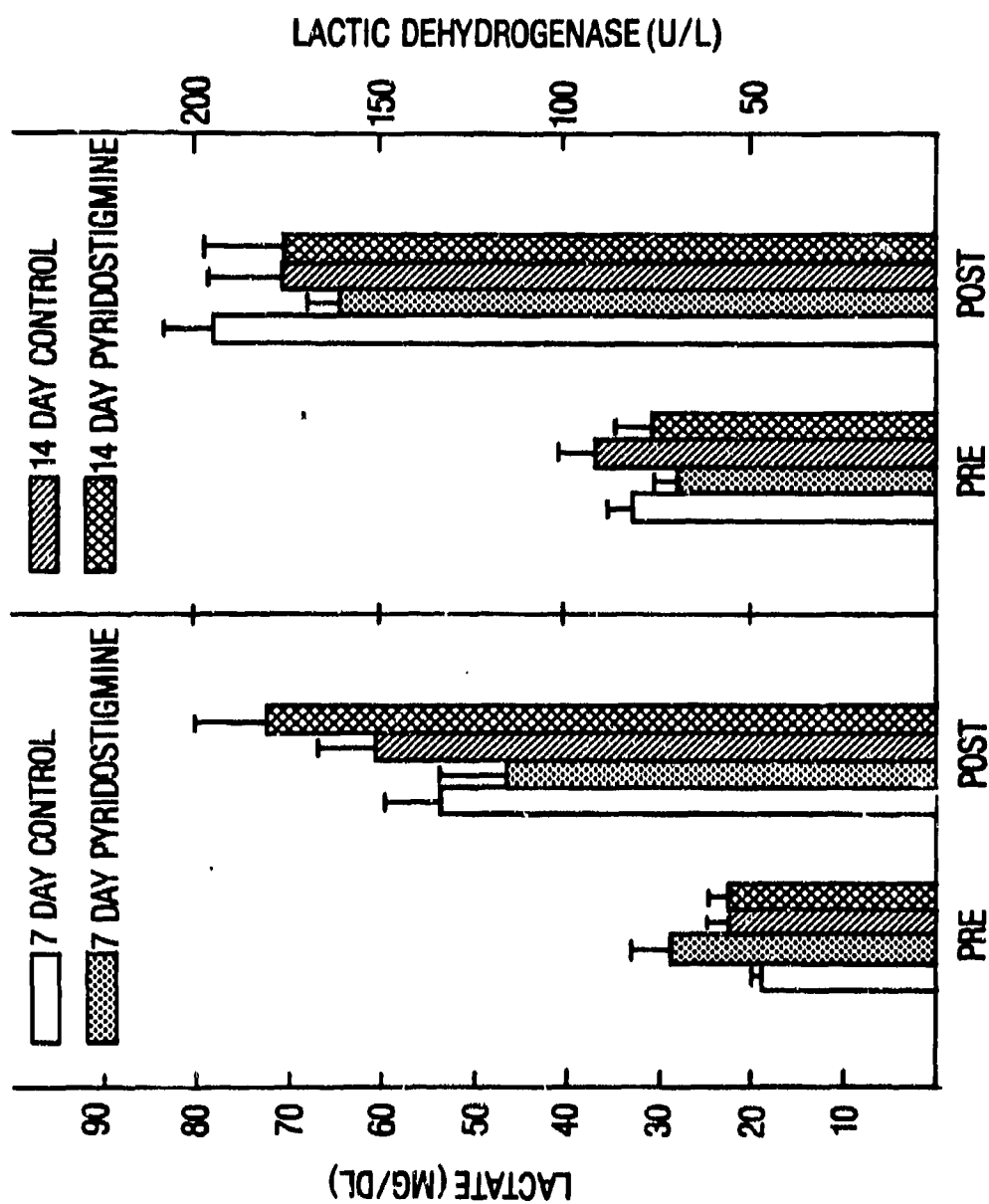
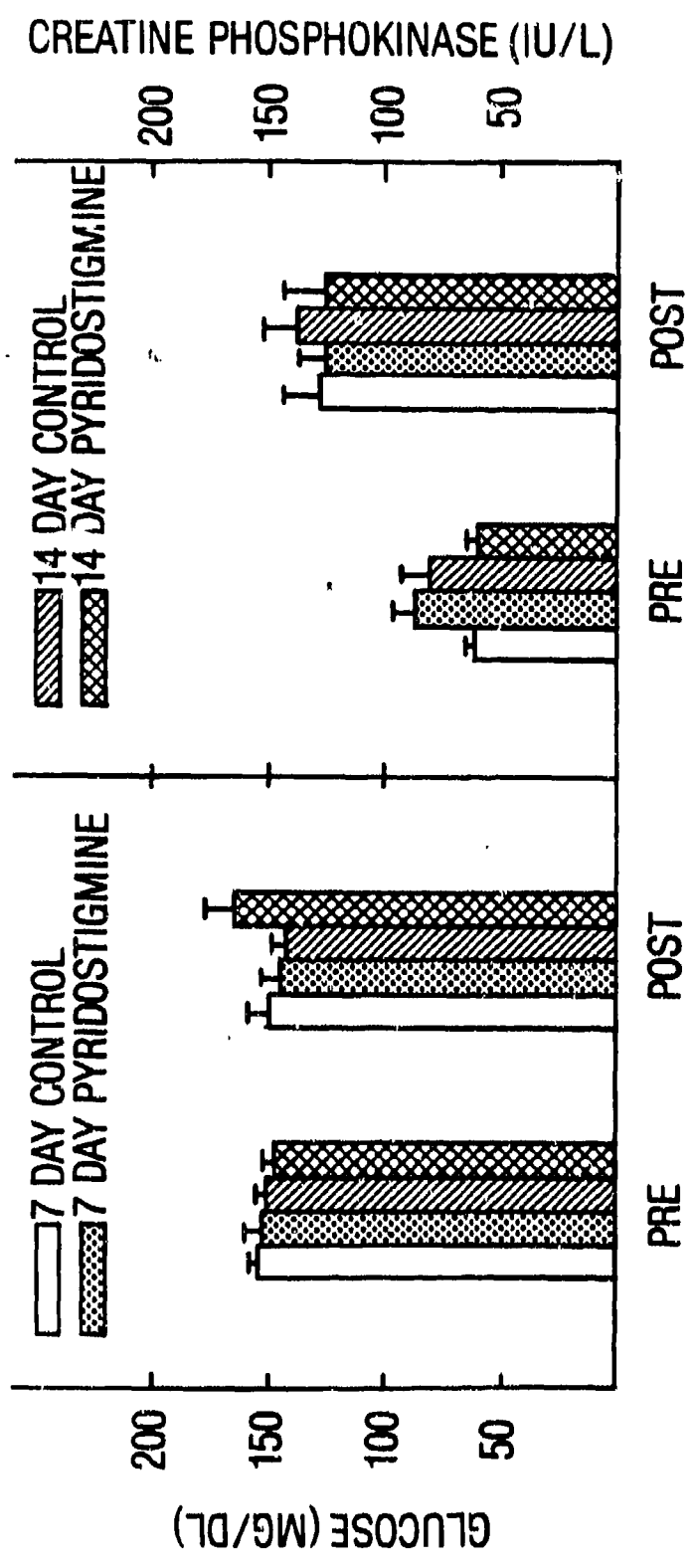


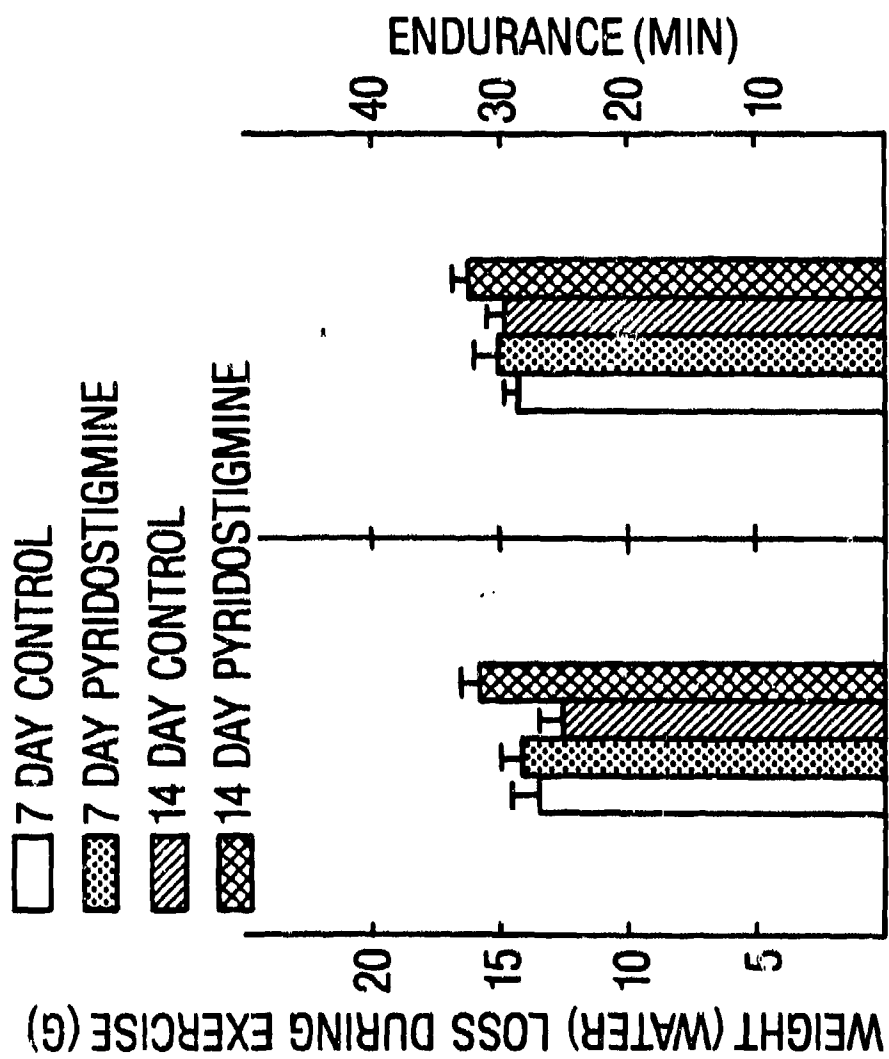
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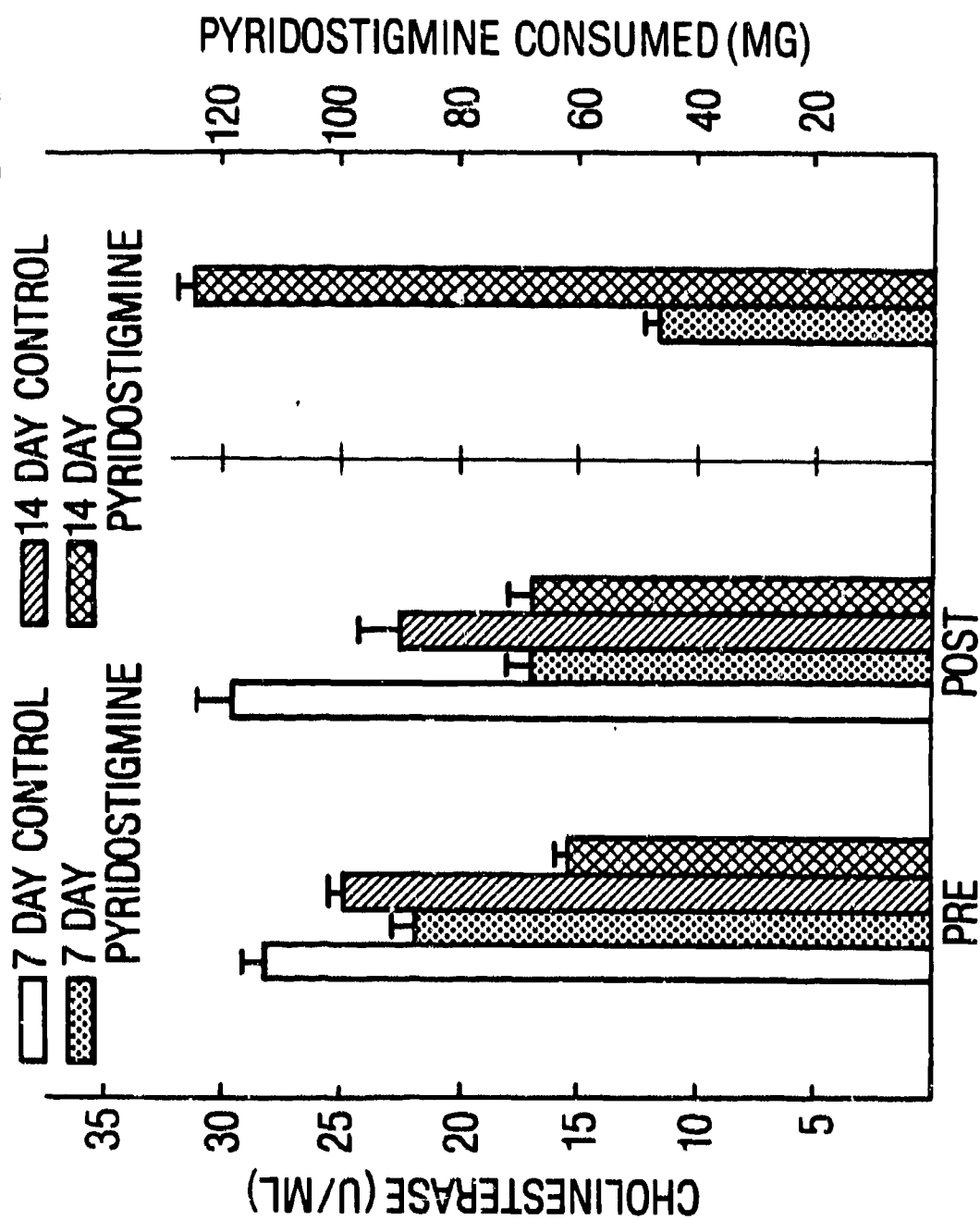
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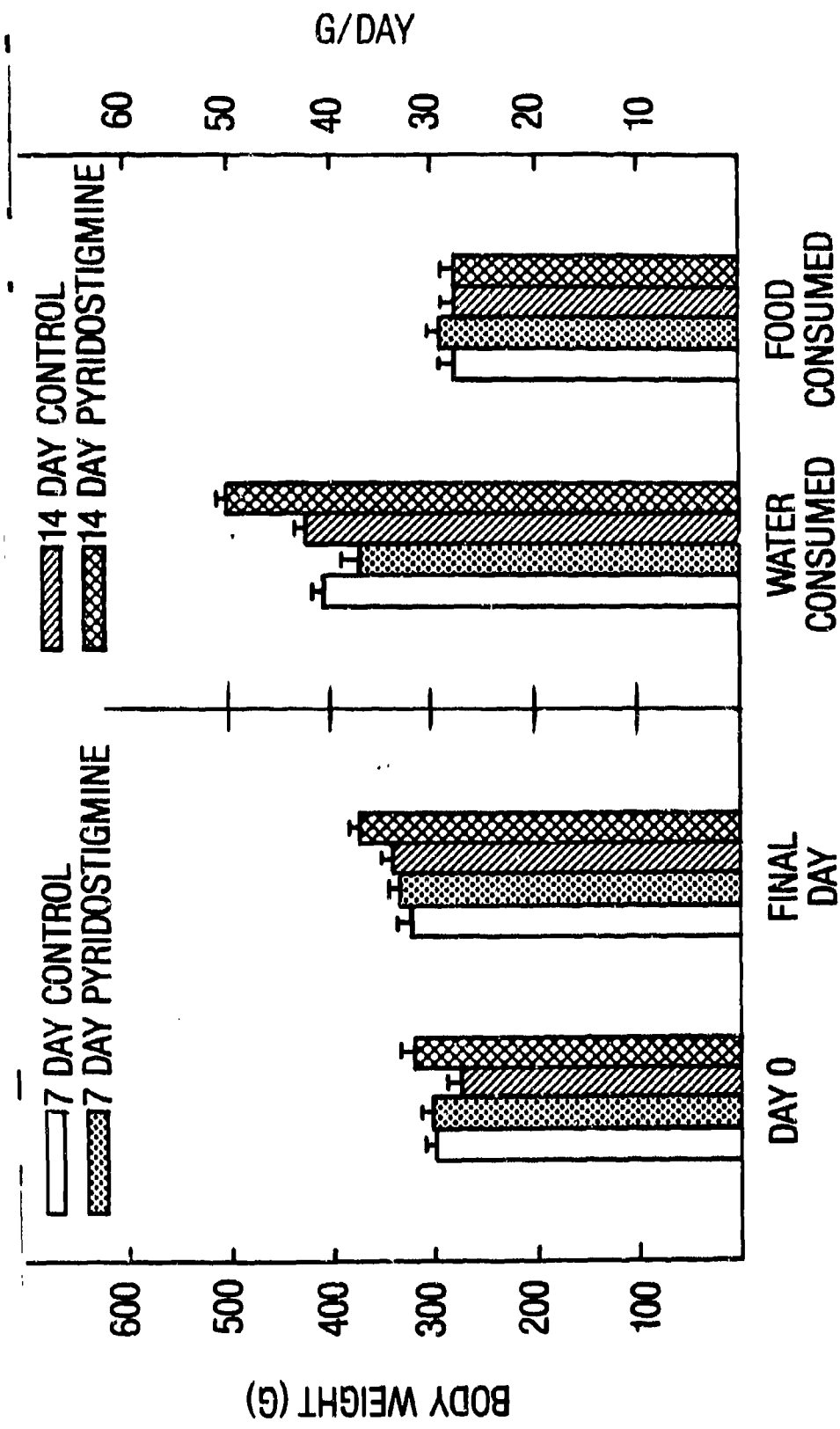
Frequently Asked



Francis et al. 1973



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Pyridostigmine 150 mg